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IN SILICO DESIGN, SYNTHESIS, DFT AND ANTIMICROBIAL EVALUATION OF SOME 2,5 SUBSTITUTED 1, 3, 4 OXADIAZOLE DERIVATIVES

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Abstract

In the present study, simple fourteen 2, 5 substituted 1,3,4- oxadiazole derivatives were subjected to molecular properties prediction and drug likeness by molinspriration software. All the compounds were selected on the basis of lipinski rule and they were synthesized and screened for antimicrobial activity against four different bacterial strains *by* the disc diffusion method. *While antifungal was determined against three different strains* by the *agar well diffusion method.* Antimicrobial studies revealed that, most of the synthesized compounds showed significant activity against all the tested microorganisms at the concentration of 100µg/mL. Quantum chemical parameters like HOMO, LUMO, energy gap, global chemical descriptors were also calculated by using DFT studies to predict the stability of the compounds and correlated with their antimicrobial activity.

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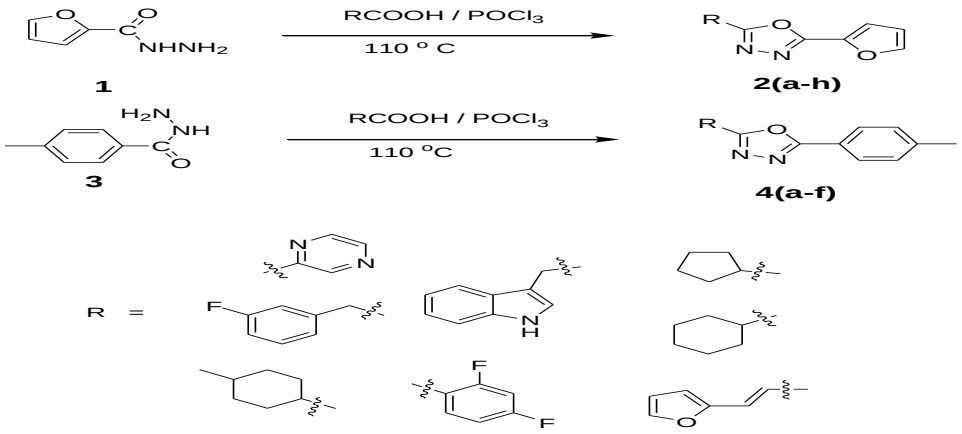
1. INTRODUCTION

Microbial infections are the common problem in all over worldwide. Now days, the occurrence of fungal and bacterial infection has been considerably increased which leads to serious health hazards [1]. Therefore, many researchers have focused their probe efforts on finding new, potent, less toxic and eco-friendly antibacterial and antifungal drugs.

Most of the heterocyclic compounds are biologically active in nature and it plays an essential role in the metabolism of all living cells[2]. Whereas, heterocyclic system also have been showing the vital role in the design and synthesis of new pharmaceutically active compounds[3].Five-member heterocycles was found to be bioactive compounds. Among them, 1,3,4-oxadiazoles acts as scaffolds in the field of therapeutic chemistry due to potent pharmacological activities. The 1,3,4-oxadiazole derivatives represent several biological activities such as antimicrobial[4], anticancer[5], anti-HIV[6], antitubercular[7], analgesic[8], anti-inflammatory[9], anticonvulsant[10], inhibition of tyrosinase[11]. On the other hand, the furan derivatives are significant heterocycle found to exhibit diverse biological activities and are also useful in stomach, renal, billiard and colic disorders. Keeping a view of the above- mentioned importance of oxadiazole and furan, the present study attempt was made to incorporate the furan with 1,3,4-oxdiazoles moieties in a single molecular framework to synthesize the linked heterocycles for enhancing the biological activity. In the present study, we report molecular prediction, DFT, synthesis and antimicrobial screening of 2,5disubstituted 1,3,4-oxadiazole derivatives.



Scheme 1: Synthetic route of di substituted 1,3,4-oxadiazole derivatives

2. MATERIAL AND METHODS

All the reagents, chemicals and solvents were purchased from Sigma-Aldrich. Melting points were determined using an open capillary method and were uncorrected. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker 300 MHz NMR spectrometers (AVANCE II) and chemical shifts were expressed as δ (ppm) with tetramethylsilane (TMS) as the internal standard. Synthetic reactions were monitored with the help of Thin layer chromatography (TLC) was performed with Merck silica gel plates and visualized with UV irradiation (254 nm) or iodine. Synthesized compounds purity was checked by TLC silica -coated plates obtained from Merck. The IR spectra were recorded on Perkin-Elmer RX I spectrometer with KBr. Mass spectrum were obtained from Waters UPLC-UPD mass spectrometer using electro spray ionization.

2.1. MOLECULAR PROPERTIES AND DRUG LIKENESS

Molecular properties and oral bioavailability are related with molecular descriptors like molecular weight, hydrogen bond and accepters in molecules, partition coefficient (log p). The entire titled compounds meet the Lipinski rules of

five showed most of these compounds obey the rules that is not problem with oral bioavailability. Compounds did not violate Lipinski's rule of five. Molecular lipophilicity is represented by partition coefficient or log p. Log p value of most of the titled compounds was found to be less than five and suggesting good permeability across the cell membrane. Molecular weight of all the synthesized compounds was found to be less than five hundred and thereby these compounds are predictable to be easily transported, diffused, and absorbed than compared with the large molecules. Solubility in water can be considered as the number of hydrogen donors in molecules. Higher amount of hydrogen bond donor translates higher amount of water solubility which in turn leads to high absorption into the blood and action. Number of hydrogen bond acceptors (notably O and N atoms) number of hydrogen bond donors of all the synthesized compounds were in agreement with the Lipinski's rules (less 10 and 5 respectively).[12] It was observed that among all 1, 3, 4-oxadiazole derivatives are like to be orally active as they obeyed Lipinski's rule of five. Numbers of rotatable bands are important for conformational changes of the molecules. The oral bioavailability criteria, number of rotatable bands should be less or equal to ten. The compounds from the series have number of rotatable bands are 2 to 4, consequently showed large conformational flexibility.[13] Topological polar surface area (TPSA) is correlated with hydrogen bonding of a drug molecule. Topological polar surface area is very good indicator of the bioavailability of the drug molecules. TPSA of 1, 3, 4-oxadaizole derivatives were observed in the range of 38.92 to 104.13 A^0. The percentages of absorption (%ABS) for entitled compounds calculated from TPSA ranged between 73.07 and 95.57 % indicated all the compounds showed moderate to excellent oral bioavailability. Molecular prediction parameters of the synthesized compounds are presented in table 1.

Table 1 Molecular prediction parameters of the titled compounds (2a-2h and 4a-4f)

Compound Code	% ABS	TBSA	volume	*n*OA	*n* ON	n OHNH	*n* violation	*n* rotb	milogp	MW
2a	91.04	52.06	200.27	16	4	0	0	2	2.39	218
2b	91.04	52.06	183.47	15	4	0	0	2	1.89	204
2c	91.04	52.06	203.42	18	4	0	0	3	2.58	244.2
2d	85.59	67.86	227.46	20	5	1	0	3	2.61	265
2e	82.14	**77.85**	173.37	16	6	0	0	2	1.04	214
2f	91.04	52.06	191.55	18	4	0	0	2	3.12	248
2g	73.07	**104.13**	297.8	26	8	0	0	4	1.58	352
2h	86.51	65.20	190.67	17	5	0	0	3	1.96	228
4a	95.57	38.92	235.26	18	3	0	0	2	3.70	242
4b	95.57	38.92	218.46	17	3	0	0	2	3.19	228
4c	95.57	38.92	238.41	20	3	0	0	3	3.89	268
4d	90.12	54.72	262.46	22	4	1	0	3	3.92	289
4e	86.67	64.71	208.36	18	5	0	0	2	2.35	238
4f	91.04	52.06	225.66	19	4	0	0	3	3.27	252

Where : miLog P = Logarithm of partition coefficient between n-octanol and water, TPSA = Topological polar surface area n-ON = Number of hydrogen bond acceptors, n-OHNH = Number of hydrogen bond donors, n-rotb Number of rotatable bonds, (%ABS) = Percentage of absorption and MW = molecular weight

The bioactivity score of the synthesized compounds for drug targets were also predicted by using molinspiration software and are depicted in table 2. A molecule having bioactivity score more than 0.00 showed significant biological

activities, if score in between -0.50 and 0.00 are expected to be moderately active. If bioactive score less than -0.50 it is considered as inactive. The results reported clearly that physiological actions of 1,3,4-oxadiazole derivatives might involve multiple mechanisms and could be due the interactions with GPCR ligands, nuclear receptor ligands, and also inhibit protease and other enzymes. The bioactivity score of all titled compounds showed moderate to good interaction with all drug targets.

Table 2 Bioactivity score of the synthesized compounds (2a-2h and 4a-4f)

Compound code	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
2a	-0.46	-0.69	-0.85	-0.98	-0.52	-0.33
2b	-0.45	-0.73	-0.90	-0.99	-0.69	-0.30
2c	-0.44	-0.70	-0.76	-0.81	-0.52	-0.27
2d	**0.04**	-0.50	-0.30	-0.53	-0.24	-0.01
2e	-0.38	-0.55	-0.60	-1.13	-0.79	-0.24
2f	-0.43	-0.77	-0.68	-0.72	0.66	-0.30
2g	-0.08	-0.41	-0.30	-0.36	-0.05	-0.14
2h	-0.85	-1.12	-1.07	-1.24	-1.00	-0.42
4a	-0.28	-0.41	-0.30	-0.48	-0.28	-0.14
4b	-0.26	-0.42	-0.31	-0.46	-0.42	-0.10
4c	-0.29	-0.47	-0.28	-0.40	-0.31	-0.13
4d	**0.10**	-0.31	0.06	-0.20	-0.09	-0.08
4e	-0.20	-0.28	-0.08	-0.61	-0.52	-0.07
4f	-0.67	-0.90	-0.62	-0.84	-0.84	-0.33

3. EXPERIMENTAL

3.1. General method for preparation of test compounds (2a–h)

Equimolar mixtures of furan 2- carbohydrazide with different carboxylic acids were refluxed with phosphorous oxy chloride (10 Vol) for 2–3 hrs. Reaction mixture was concentrated through rotatary evaporator, the residue was quenched with ice water, washed with sodium hydrogen carbonate, and the solid separated was filtered off, washed with water, cold ethanol to give 1,3,4 oxadiazole derivatives.(Scheme1) as per reported procedure. [14-15]

3.2. General method for Synthesis of test compounds (4a-f)

Equimolar mixtures of 4-methyl benzhydrazide with different carboxylic acids were refluxed with phosphorous oxy chloride (7 Vol) for 2–4 hrs. Reaction mixture was concentrated through rotatary evaporator, the residue was quenched with ice water, washed with sodium hydrogen carbonate, and the solid separated was filtered off, washed with water, cold ethanol to give 1,3, 4 oxadiazole derivatives.[14-15]

3.3. 2-cyclohexyl-5-(furan-2-yl)-1, 3, 4-oxadiazole (2a)

Pale yellow solid, mp 100^{o} C; yield 78%. IR (KBr, cm^{-1}): 1410, 1450, and 1520 (for oxadiazole) 1630(C=N), 1018(C-O-C), 1536 (C=C), 1354 (C-N Str) and 2931, 2857(CH_2 Str). ^{1}H NMR ($CDCl_3$,300MHz): δ 1.79-2.13 (10H, m), 2.94-

2.99(m, 1H),6.56-6.57(1H, m), 7.10-7.11(1H, d),7.60-7.61(1H, d). C^{13} NMR ($CDCl_3$, 300MHz): δ 165.4, 154.8, 151.3, 147.3, 116.4, 112.7, 35.2, 30.1, 29.2, 25.4. LC/ESI: m/z value 219 (M+1).

3.4. 2-cyclopentyl-5-(furan-2-yl)-1,3,4-oxadiazole (2b)

Brown solid, mp 86° C; yield 81%.IR (KBr, cm^{-1}): 1410, 1452, and 1527 (for oxadiazole) 1631(C=N), 1018(C-O-C), 1566(C=C), 2959, 2874(CH_2 Str) and 1304 (C-N Str). ^1H NMR ($CDCl_3$, 300MHz): δ 1.68-2.17(8H, m), 3.32-3.41(1H, m), 6.57-6.59(1H, m), 7.12-7.13(1H,
d), 7.62 (1H, d). C^{13} NMR ($CDCl_3$, 300MHz): δ 165.9, 153.5, 151.3, 145.1, 115.9, 111.7, 37.2, 32.1, 23.7. LC/ESI: m/z value 205 (M+1).

3.5. 2-(2-fluorobenzyl)-5-(furan-2-yl)-1, 3, 4-oxadiazole (2c)

Brown solid, mp 92° C; yield 75%.IR (KBr, cm^{-1}): 1452, 1492, and 1517 (for oxadiazole) 1629 (C=N) ,1011(C-O-C), 1581 (C=C) ,1357 (C-N Str), 2927, 2856(,CH_2 Str,), 3039 (Ar-H mono substituted), 754(C-H bend) , 1229(C-F Str).^1H NMR ($CDCl_3$, 300MHz): δ 4.30(s, 2H),6.56-6.57(m, 1H), 7.05-7.15(m, 3H), 7.26-7.34(m, 2H), 7.60-7.61(m, 1H). C^{13} NMR ($CDCl_3$, 300MHz): δ 165.7, 161.8, 157.3, 154.1, 140.3, 131.8, 127.4, 124.7, 124, 113.4, 107.2, 34.5. LC/ ESI: m/z value 245(M+1)

3.6. 2-((1H-indol-3-yl) methyl)-5-(furan-2-yl)-1,3, 4-oxadiazole (2d)

Orange solid, mp110°C; yield 72%.IR (KBr, cm^{-1}): 1452, 1517and 1563 (for oxadiazole) 3368(N-N Str for indole), 1630(C=N),1012(C-O-C), 2923, 2855(CH_2 Str), ^1H NMR ($CDCl_3$, 300MHz): δ 4.41(s, 2H),7.06-7.07(m, 1H),7.13-7.22(m, 3H),7.37(d, 2H, *J* = 6Hz),7.58(d,1H)7.68(d, 1H, *J* = 5.7Hz) ,8.45(s, 1H, NH).C^{13}NMR($CDCl_3$, 300MHz): δ 165.8, 157.3, 147.7, 137.6, 135.8, 127.8, 120.5, 120.3, 116.7, 114.1, 111.7, 30.5. δ LC / ESI: m/z value 266(M+1)

3.7. 2-(furan-2-yl)-5-(pyrazin-2-yl)-1, 3, 4-oxadiazole (2e)

Pale Yellow solid, mp 152° C; yield 85%.IR (KBr, cm^{-1}):1418, 1452 and 1520 (for oxadiazole) 1616(C=N) 1012(C-O-C), 2924, 2856(CH_2 Str), 3119 (Ar-H), ^1H NMR ($CDCl_3$, 300MHz): δ 6.67-6.65(1H, m), 7.71-7.72(1H, d), 7.36(1H, dd, *J* = 4.8Hz), 8.77(2H, m, *J* = 1.6Hz), 9.53(1H, d, *J* = 1.6Hz). C^{13} NMR ($CDCl_3$, 300MHz): δ 162.7, 157.3, 152, 147.2, 145.1, 141.8, 140.7, 139.6, 116.8, 112.3.LC/ ESI: m/z value 215(M+1)

3.8. 2-(2, 5-difluorophenyl)-5-(furan-2-yl)-1, 3,4-oxadiazole (2f)

White solid, mp 127°C; yield 79%.IR (KBr, cm^{-1}):1442, 1518 and 1555 (for oxadiazole) 1629(C=N) 1008 (C-O-C), 2923, 2856 (CH_2 Str), 3079 (Ar-H), 1235 (C-F Str), 864,767(Meta di substituted).^1H NMR ($CDCl_3$, 300MHz): δ 6.65(dd, 1H, *J* = 2.2, 3.7Hz), 7.01(tt, 1H, *J* = 1.9Hz), 7.23(d, 1H),7.64-7.702(m, 3H).C^{13}NMR($CDCl_3$,300MHz):δ 165.5, 160.8, 158.4, 157.5, 139.5, 129.6, 119.8, 118.3, 116.7, 114.8 , 113.9. LC/ ESI: m/z value 249(M+1).

3.9. 4-bis (5-(furan-2-yl)-1,3 4-oxadiazol-2-yl)cyclohexane (2g)

Pale yellow solid, mp 118° C; yield 72%.IR (KBr, cm^{-1}):1452, 1518 and 1564 (for oxadiazole) 1635(C=N) 1015(C-O-C), 2923, 2858(CH_2 Str), (^1H NMR ($CDCl_3$, 300MHz): δ 1.79-1.87(m, 2H), 2.01-2.07(m, 2H), 2.21-2.40(m, 4H), 3.01-3.25(m, 2H), 6.56-6.59(m, 2H),7.12-7.14(m, 2H),7.61-7.62(m, 2H).C^{13}NMR ($CDCl_3$,300MHz):δ 170.2, 157.8, 149.6, 138.5, 115.7, 111.3, 38.3, 35.2, 28.5. LC/ ESI: m/z value 353(M+1).

3.10. 2-(furan-2-yl)-5-(2-(furan-2-yl) vinyl)-1, 3, 4-oxadiazole (2h)

Brown solid, mp 123°C; yield 69%.IR (KBr, cm^{-1}): 1518, 1455, and 1399 (for oxadiazole) 1635(C=N) 1015(C-O-C), 2926, 2855(CH_2 Str). (^{1}H NMR ($CDCl_3$, 300MHz); δ 6.43(d, 1H, *J* = 1.5Hz), 6.55 (d, 2H, *J* = 3.3Hz) ,6.85(d, 1H, *J* = 8.4Hz), 7.14(d, 1H, *J* = 3.3Hz), 7.33(d, 1H, *J* = 3.5Hz), 7.45(d, 1H),7.58(d,1H). C^{13}NMR ($CDCl_3$, 300 MHz) : δ 161.3, 157.5, 151.3, 147.8, 145.4, 139.6, 116.7, 115.1, 112.7. LC/ ESI: m/z value 229(M+1).

3.11. 2-cyclohexyl-5-(p-tolyl)-1, 3, 4-oxadiazole (4a)

White solid, mp 92°C; yield 82%.IR (KBr, cm^{-1}):1496, 1445 and 1410 (for oxadiazole) 1592(C=N), 1014 (C-O-C), 2933, 2855(CH_2Str). ^{1}HNMR ($CDCl_3$, 300MHz):δ 1.26-1.47(3H, m),1.63-1.78(3H, m), 1.86-1.91(2H, m), 2.12-2.18(2H, m), 2.46(S, 3H), 2.9-3.04 (m, 1H), 7.32(d, 2H, *J* = 7.8 Hz), 7.92(d, 2H, *J* = 8.1Hz).^{13}NMR($CDCl_3$ 300MHz): δ 168.6, 163.3, 140.9, 128.8, 125.7,128.3, 120.3,41.9,39.4,38.5,34.1,29.1,21.5.LC/ESI: m/z value 243(M+1).

3.12. 2-cyclopentyl-5-(p-tolyl)-1, 3, 4-oxadiazole (4b)

Brown crystalline, mp 85°C; yield 73%.IR (KBr, cm^{-1}):1498, 1448 and 1401 (for oxadiazole) 1605(C=N), 1012(C-O-C), 2954, 2870 (CH_2 Str). ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.64-2.13(m, 8H), 2.34(s, 3H), 3.25-3.36(m, 1H), 7.15-7.27(d, 2H), 7.93-7.96(d, 2H). C^{13}NMR ($CDCl_3$, 300 MHz :170.2, 163.7, 138.7, 133.4, 128.4, 125.9, 37.5, 32.2, 23.1, 21.5.LC/ESI: m/z value 229(M+1).

3.13. 2-(3-fluorobenzyl)-5-(p-tolyl)-1, 3, 4-oxadiazole (4c)

Pale yellow solid, mp 92°C; yield 78%.IR (KBr, cm^{-1}):1491, 1456 and 1411 (for oxadiazole) 1595(C=N) 1010(C-O-C), 3029, 2933 (CH_2 Str). ^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.32(s, 3H), 4.21(s, 2H),6.97-7.14(m, 3H), 7.23-7.28(m, 4H), 7.94(d, 2H, *J* = 8.1Hz). C^{13}NMR ($CDCl_3$, 300 MHz):165.5, 163.8, 161.5, 139.7, 136.5, 129.7, 128.6, 126.8, 123.4, 121.5, 117.4, 112.7, 33.9, 21.3 .LC/ ESI: m/z value 269(M+1).

3.14. 2-((1H-indol-3-yl) methyl)-5-(p-tolyl)-1,3,4-oxadiazole (4d)

Dark brown solid, mp 110°C; yield 56%.IR (KBr, cm^{-1}):1495, 1455 and 1420(for oxadiazole) 1606(C=N) 1010(C-O-C), 3049, 2923(CH_2 Str), (^{1}H NMR ($CDCl_3$, 300MHz): δ 2.34 (s, 3H), 4.34(s, 2H), 7.02-7.17(m, 1H), 7.15-7.18(m, 3H), 7.26(d, 1H, *J* = 8 Hz), 7.33(d, 1H, *J* = 8.1Hz),7.65(d, 1H, *J* = 7.8Hz), 7.79(d, 2H, *J* = 8.1Hz), 7.94(d, 1H, *J* = 8.1Hz), 8.21(s, 1H). C^{13}NMR ($CDCl_3$, 300 MHz) : 165.6, 163.9, 139.8, 137.4, 135.7, 129.6, 127.8, 126.8, 123.9, 122.2, 120.5, 120.3, 111.7, 104, 31.2, 21.6. LC/ ESI: m/z value 276(M+1)

3.15. 2-(pyrazin-2-yl)-5-(p-tolyl)-1,3, 4-oxadiazole(4e)

Yellow solid, mp 73°C; yield 83%.IR (KBr, cm^{-1}): 1489, 1453, and1419 (for oxadiazole), 1606(C=N), 1015 (C-O-C), 2923, 2855 (CH_2 Str). ^{1}H NMR ($CDCl_3$ 300 MHz) : δ 2.3(s, 3H), 7.28 (d, 2H, *J* = 8.4Hz), 8.02(2H, d), 8.70(m, 2H), 9.45(d, 1H, *J* = 1.2Hz). C^{13}NMR ($CDCl_3$, 300 MHz) : 165.6, 162.2, 152.3, 145.4, 141.8, 140.7, 139.7, 128.9, 126.2, 123.9, 21.3. LC/ESI: m/z value 239(M+1).

3.16. 2-(2-(furan-2-yl) vinyl)-5-(p-tolyl)-1,3,4-oxadiazole(4f)

Brown solid, mp 85°C; yield 65%. IR (KBr,cm^{-1}) : 1581,1491 and1456 (for oxadiazole) 1625(C=N), 1007(C-O-C), 2966, 2855 (CH_2 Str), ^{1}HNMR ($CDCl_3$,300MHz): δ 2.36 (s,3H),6.430(m, 1H, J= 3.3, 1.8 Hz), 6.54 (d, 1H, *J* =3.3Hz), 6.89 (d, 1H, *J* = 16.2Hz), 7.25 (d, 2H, *J* = 8.1Hz), 7.30 (d, 1H, *J* = 16.2Hz), 7.45 (d, 1H, *J* = 1.5Hz) ,7.91 (d,

2H, *J* = 8.1Hz). C^{13}NMR ($CDCl_3$, 300 MHz) : 166.5, 164.6, 152.2, 145.6, 139.7, 131.5, 129.3, 126.8, 123.8, 115.3, 112.7, 21.5. LC/ ESI: m/z value 253(M+1).

4. BIOLOGICAL SCREENING

4.1 . ANTIBACTERIAL STUDIES

Antibacterial activity of all the synthesized compounds (2a-h) and (4a-f) was determined by disc diffusion method [16]against two kind of gram positive micro organisms *Staphylococcus aureus* (MTTC 25932), Bacillus substilis (MTTC 10619) and two gram negative micro organisms, *Escherichia coli (MTTC* 1987), Pseudomonas *aeruginosa (MTTC* 1687*) at concentrations of 100 µg/mL using DMSO as a solvent. It was screened with a Mueller Hinton agar medium (MHA) obtained from Himedia (Mumbai) for bacterial growth. Streptomycin is used as standard and the zone of inhibition was measured for 24 hr at* 37^0*C.*

4.2 ANTIFUNGAL STUDIES

All the synthesized compounds were evaluated for their in vitro antifungal activity such as A. Niger (MTTC 1344); C. Albicans (MTTC 227), *S.Flavus (MTTC* 2729) *using agar well diffusion method*[17]*. Fucanazole was used as the standard and positive control. All the synthesized compounds and standard were used at different concentrations like 40, 60, and 100 µg/ mL. The fungi were sub-cultured on Sabouraud Dextrose broth and the fungal plates were incubated at* 37^0 *C for 72 hours.*

5. *RESULT AND DISCUSSION*

5.1 .CHEMISTRY

Oxadiazole derivatives were synthesized by using commercially available furan-2- carbohydrazide *and 4- methyl benzhydrazide. These synthesized compounds were prepared according to reported procedure. FT-IR spectrum of compounds exhibited absorption wavelength at 1595-1635* cm^{-1}*due to C=N group, another band at 1007-1018* cm^{-1}*due to C-O-C group. In general,* H^1 *NMR spectrum of oxadiazole derivatives showed doublet, multiplet in between δ 6.43- 9.45 ppm due to the presence of aromatic protons. Similarly, a singlet was appeared at δ 2.30-2.46 ppm due to three protons for methyl group. The mass spectrums of the compounds were in full agreement with their respective molecular weight of compounds. The structure of all synthesized compounds were confirmed the basis of IR,* H^1 *and* C^{13} *NMR, Mass spectral studies.*

5.2. *COMPUTATIONAL STUDIES*

Quantum chemical parameter like, E_{HOMO} , E_{LUMO} and energy gap (Δ**E**), chemical potential(µ), Dipole moment, global hardness(η), global softness(S), Electrophilic index(ω) of the all titled molecules were fully optimized by using DFT by RB3LYP(2d, p) with electron basis set 6-311++G Gaussian 09 [18]and also Clog P were calculated using Chem draw ultra 7.0. *Quantum chemical descriptors like chemical hardness (η), chemical softness, chemical potential, electrophilic index are determined by using DFT calculations. Global hardness (η) is related with the reactivity and stability of the molecules. According to the Frontier molecular orbital theory, chemical hardness is associated with the energy gap between energy of highest occupied molecular orbital and the lowest unoccupied molecular orbital. It is measured by the following equation (1)*

$$\eta = (E_{LUMO} - E_{HOMO}) / 2 \qquad (1)$$

From the table (**III**) it was concluded that a molecule with a high energy gap (ΔE) is less polarizable and associated with a low chemical reactivity. In the first series, Compound 2c has highest energy gap value, low chemical reactivity,

and highest chemical hardness value by DFT studies. The decreases in LUMO value and increase HOMO increase the chemical reactivity of synthesized compounds and decrease their antimicrobial activities against tested micro organisms. The low chemical hardness of the compounds is less stable and more reactive. Thereby, among the fourteen synthesized compounds, compound **4d** is more reactive than others the tested compounds. Furthermore, the compound **4d** has less hard. Chemical softness (S) is measured as reciprocal of the hardness of the molecules. It is calculated by given equation (2). Compound 4d acts as soft molecule and it has small energy gap and more reactive all among the synthesized compounds.

$S = 1 / 2\eta$ (2)

Chemical potential (μ) is measured by negative value of the electro negativity of the molecules and the escaping tendency of the electrons from the equilibrium state. Chemical potential is determined using the following the equation (3). Compound 2c has the highest chemical potential, least reactive and most stable. Furthermore compound 2c has more antimicrobial activity.

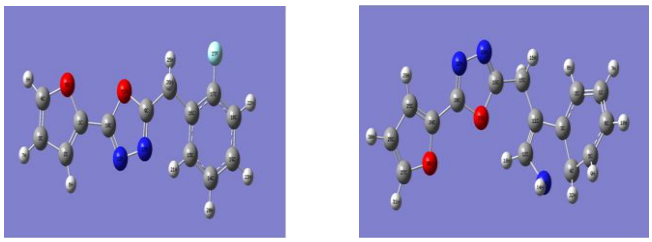
$H= (E_{LUMO} + E_{HOMO)}) / 2$ (3)

Electrophilic index (ω) is positive value and the direction of the charge transfer is fully calculated by chemical potential and chemical hardness of the molecules.

Table 3 Quantum chemical descriptors for compounds determined using by RB3LYP/6-311G (d,p).

Compound	E_{HOMO}	E_{LUMO}	ΔE	μ	μ (D)	η	S	ω	C log P
2a	-0.15805	-0.10642	-0.05163	-0.13223	2.8007	0.02518	19.85	0.34751	2.318
2b	-0.24049	-0.05747	-0.18302	-0.14898	2.1128	0.09151	5.463	0.1212	1.759
2c	-0.24133	-0.06688	-0.30821	-0.15411	2.6229	0.15410	3.245	0.0770	2.138
2d	-0.28074	-0.07341	-0.20733	-0.17705	2.3544	0.10366	4.823	0.1511	1.755
2e	-0.24480	-0.08611	-0.15869	-0.16545	2.4890	0.07934	6.3019	0.1724	-0.03
2f	-0.32943	-0.05143	-0.2780	-0.19043	2.0061	0.1390	3.597	0.1304	2.345
2g	-0.32493	-0.07786	-0.24707	-0.20139	0.7769	0.12353	4.047	0.1641	1.282
2h	-0.14816	-0.06552	-0.08264	-0.10684	1.1088	0.04132	12.1006	0.1381	1.796
4a	-0.19319	-0.09224	-0.10010	-0.14271	3.4205	0.05005	9.99	0.2034	3.431
4b	-0.24205	-0.05994	-0.18211	-0.15099	3.1544	0.09105	5.491	0.1251	2.872
4c	-0.23995	-0.06366	-0.17629	-0.15180	2.7683	0.08814	5.6727	0.13071	3.021
4d	-0.12636	-0.11651	-0.0099	-0.12143	5.1533	0.00495	101.01	**1.4894**	2.868
4e	-0.24364	-0.08225	-0.16139	-0.16294	3.1946	0.08069	6.1965	0.16419	1.082
4f	-0.14331	-0.06141	-0.0819	-0.10236	1.5162	0.04095	12.21	0.12796	2.909

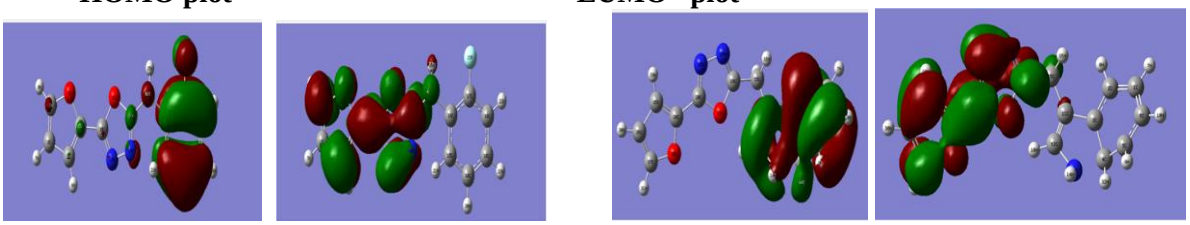
The results of electrophilic index showed that compound **2c** is a strongest nucleophile and compound **4d** act as strongest electrophile. Energy gap, chemical reactivity, lipophilicity, chemical hardness and softness are important parameters on biological activity of the synthesized molecules. Furthermore, the chemically reactive compounds are not suitable for the biological activity. The compounds have the lower values of C log p may be enhance biological activities and were calculated using Chem Draw software 7.0 [17].



Compound 2c **Compound 2d**

Figure 5.3 Optimized structures of the compounds 2c and 2d

HOMO plot **LUMO plot**



Compound 2c **Compound 2d**

Figure 5.3 HOMO-LUMO energies of synthesized compounds 2c and 2d

*5.3.**IN VITRO ANTIBACTERIAL SCREENING***

***Table** -4 The zone of the inhibition for the compounds against different microorganisms*

Compound Code	Diameter of Zone of Inhibition in mm						
	Gram positive Bacteria		**Gram negative Bacteria**		**Antifungal**		
	SA	**BS**	**EC**	**PA**	**CA**	**AN**	**AF**
2a	18	20	29	21	22	18	17
2b	23	17	24	22	25	25	17
2c	23	24	26	20	20	22	25
2d	19	25	25	24	26	26	23
2e	16	12	16	15	14	14	11
2f	15	14	16	25	15	15	14
2g	10	11	18	15	17	17	17
2h	12	10	13	12	15	15	16
4a	11	16	13	14	16	16	15
4b	13	15	13	13	15	15	16
4c	15	18	15	16	18	18	18
4d	13	11	12	11	10	17	12
4e	17	15	14	16	16	16	15
4f	15	14	16	14	18	18	16
Chloromphenical	**24**	**25**	**23**	**26**			
Flucanazole					**24**	**27**	**23**

The newly synthesized compounds (2a–h) and (4a-f) were tested for their antibacterial activity in vitro against *E. coli, S. aureus and P. aeruginosa, B.subtilis* and their activity was compared to a known antibiotic as chloramphenicol. Antibacterial activity was determined by the disc diffusion method by measuring its zone of inhibition. Many of the

synthesized compounds showed moderate to good inhibition against all tested organisms. While the compounds 2a, 2b, 2c and 2d exhibited excellent antibacterial activity at concentration of 100µg/ mL. Whereas compounds 2e, 2f, 4c, 4e and 4f showed good activity compared with the standard. *The results of antimicrobial assay are given in table –IV.*

5.4. *IN VITRO ANTIFUNGAL SCREENING*

The above same compounds (2a-h) and (2a-f) are tested for antifungal activity against C.Albicans, A.Niger and A.Flavous at various concentrations of 100µg/mL as shown in table IV. Among the newly synthesized compounds are considerable inhibitions against all of the tested fungi. *Result revealed that most of the synthesized compounds showed good inhibition against the tested fungi. Particularly, compounds 2c and 2d showed excellent antifungal activity.*

6. CONCLUSION

Fourteen 1,3,4-oxadiazole derivatives were obey lipinski rule of five and were synthesized and tested for their antibacterial and antifungal studies. Five compounds exhibited promising activity against tested all microorganisms at concentration of 100µg/ ml. While the other compounds also showed moderate antimicrobial activity. Particularly, compounds 2-(2-fluorobenzyl)-5-(furan-2-yl)-1,3,4-oxadiazole and 2-((1H-indol-3-yl) methyl)-5-(furan-2-yl)-1,3,4-oxadiazole were found to effective antimicrobial agent. The SAR study revealed that furan substituted with 1,3,4-oxadiazole ring may be enhance antimicrobial activity. It is also confirmed by DFT calculations and could be also helpful in synthesis of more suitable drugs in medicinal chemistry.

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